Medicines & Healthcare products Regulatory Agency

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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First, we advise healthcare professionals that codeine linctus cough medicines have been reclassified to a prescription-only medicine (POM), following a public consultation.

Our second article informs healthcare professionals of very rare reports of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) with pseudoephedrine. Patients and caregivers should be advised to be alert to the symptoms for PRES and RCVS, to stop the medication immediately and to seek urgent medical attention if these occur. If someone presents with symptoms of PRES or RCVS, ask about their medication history.

Our final article provides a summary of recent letters and notifications sent to healthcare professionals about medicines.

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Codeine linctus (codeine oral solutions): reclassification to prescription-only medicine

Advice for healthcare professionals on the reclassification of codeine linctus to a prescription-only medicine (POM), following a public consultation.

Advice for healthcare professionals:

- codeine linctus is to be reclassified from a pharmacy-only medicine (P) to a prescription-only medicine (POM) owing to the risk of dependence, addiction, and overdose
- codeine linctus is only authorised for the treatment of dry cough
- codeine linctus is only considered to be effective in the treatment of chronic cough lasting over 8 weeks[1]
- advise patients that those with a long-term cough should see a healthcare professional, for review of symptoms and may require medical assessments to check for other conditions which may be the cause of the cough
- we would encourage healthcare professionals to read the Summary of Product Characteristics for special warnings and contraindications for the use of codeine linctus, especially in patients with a history of substance abuse
- record prescription details in the patient's summary care record (or equivalent) and encourage patients to read the Patient Information Leaflet that comes with their medicine
- report suspected adverse drug reactions to codeine linctus to the Yellow Card scheme

Advice for healthcare professionals to provide to patients, parents and carers:

- codeine linctus (also known as codeine oral solution) is used in the treatment of dry cough, in adults and children aged 12 to 18 years without breathing difficulties
- codeine is an opioid medicine and is addictive. Codeine linctus will only be available on prescription following assessment with a healthcare professional. This action is being taken to reduce the risk of addiction or overdose
- evidence is limited that codeine linctus is effective in the treatment of short-term cough but may be effective in the treatment of long-term cough (lasting over 8 weeks)
- alternative non-prescription cough medicines are available for short-term cough to sooth an irritated throat, including honey and lemon mixtures and cough suppressants. You can speak to a pharmacist for advice
- if you have a long-term cough, you may be asked to attend further medical assessments to check for other conditions which could be causing the cough. This is to make sure you are on the best treatment
- addiction can happen gradually especially if you have been taking codeine for a long time. If you want to stop taking it and have been taking codeine linctus for a long time, then it is important to reduce the amount you take slowly with the help of your prescriber

- if you feel that you are addicted, speak to your doctor, or if you are concerned for someone who has been using more than the prescribed amount of codeine linctus, you can also seek advice on the NHS website. Support groups and self-help groups are also available such as Talk to FRANK
- patients are urged not to buy codeine linctus from an unregistered website as it could be dangerous

Background

Codeine linctus (also known as codeine oral solution) is authorised for the treatment of dry coughs in adults and children aged 12 to 18 years without breathing difficulties. Codeine linctus is not authorised for the treatment of pain.

Codeine linctus has been used as a cough medicine for many years, although the evidence for effectiveness in short-term cough is limited.[1]

Codeine is converted into morphine by the liver enzyme CYP2D6. Some people (known as ultra-rapid metabolisers) convert codeine into morphine faster than others. Evidence indicates that morphine is effective in the treatment of chronic cough.[2] However, patients with chronic cough may have underlying conditions, and they should undergo medical investigation to establish the best treatment.

As an opioid medicine, codeine linctus is known to be addictive.

Recent review of safety of codeine linctus

Recent safety information has revealed that codeine linctus is being used recreationally for its opioid effects, rather than for its intended use as a cough suppressant. This carries a serious risk of addiction and overdose which can be fatal.

Significant concerns have been raised concerning the use of codeine linctus as an ingredient in the recreational drink known as ‘Purple Drank’ (alternative names: ‘Lean’, ‘Sizzurp’, ‘Dirty Sprite’). As codeine linctus is used in varying amounts in this drink, consumers may not be aware of how much they are taking, and this can have serious risks such as loss of consciousness, respiratory suppression and death. Concomitant use with a central nervous system (CNS) depressant, such as alcohol, sedatives or other medicines, will further increase these risks. The MHRA has found evidence of Purple Drank being popularised through social media targeting young adults and has received an increased number of reports of the sale of codeine linctus through non-regulated and potentially illicit websites. Healthcare professionals have also identified individuals repeatedly requesting codeine linctus who are potentially addicted to it.

In October 2022, the Commission on Human Medicines (CHM) advised that codeine linctus should be made available as a prescription-only medicine (POM). The MHRA undertook a public consultation to obtain views on its reclassification. The consultation ran from 18 July 2023 to 15 August 2023.

Following the results of the public consultation and the further advice of the CHM, codeine linctus will no longer be supplied without a prescription. This is a risk minimisation measure to protect the health of patients in need of treatment, to prevent recreational use and to enable the identification of individuals who may have become unintentionally addicted to codeine.

Patients will still be able to access codeine linctus with a prescription from a qualified healthcare professional. This will ensure that the medicine is used safely and appropriately under medical supervision.

Monitoring of codeine linctus side effects

The MHRA has been monitoring the risk of addiction to codeine for a number of years and regulatory action has been taken to improve product information and labelling. However, codeine linctus usage may result in dependence or addiction and we have seen abuse of this medicine when used in recreational drinks such as Purple Drank. For those who are ultra-rapid metabolisers of codeine, the risk of opioid toxicity is increased.

Opioid toxicity may resemble overdose in presentation with symptoms such as respiratory depression, pinpoint pupils, coma and death.

The consumption of codeine in recreational drinks leads to an increased risk of sedation and may cause the user to lose track of how much they have consumed.

Between January 2017 and May 2022, the National Poison Information Service received 19 calls in relation to codeine linctus, including codeine paediatric linctus, ‘Purple Drank’, ‘Lean’, ‘Sizzurp’, ‘Dirty Sprite’ and pholcodine linctus.

Data from the Office for National Statistics revealed an increase in the annual number of deaths where codeine was involved from 88 deaths in 2011 to 200 deaths in 2021. This does not include deaths where codeine was used in a compound formulation, for example, where codeine has been combined with paracetamol, but may include deaths where patients were obtaining codeine by prescription as well as non-prescription methods. It is not possible to determine how many patients have overdosed or died because of the misuse of codeine linctus itself, as case reports may simply name codeine as the implicated drug and do not specify the brand name or pharmaceutical form.

The MHRA has received 3 case reports describing addiction specifically with codeine linctus. The public have also informed us of several suspected cases of addiction through our consultation. However significant under-reporting of addiction is likely as those using codeine recreationally may be less likely to submit reports.

Report side effects, including dependence

Please continue to report any suspected adverse drug reactions through the Yellow Card scheme. If a patient experiences any side effect related to dependence to a medicine or is recognised by the prescriber to be dependent, the CHM encourages

prescribers, patients, or carers to report this to the MHRA through the Yellow Card scheme with the term ‘dependence’. Your report will help us safeguard public health.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates.

References

[1] Morice A and Kardos P. ‘Comprehensive evidence based review on European antitussives’. BMJ Open Respiratory Research 2016: volume 3, article e000137.

[2] Morice AH and others. ‘Opiate therapy in chronic cough’. American Journal of Respiratory and Critical Care Medicine 2007: volume 175, issue 4, pages 312 to 315.

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Pseudoephedrine: very rare risk of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

There have been very rare reports of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) with pseudoephedrine. Patients and caregivers should be advised to be alert to the symptoms for PRES and RCVS, to stop the medication immediately and to seek urgent medical attention if these occur. If someone presents with symptoms of PRES or RCVS, ask about their medication history.

Advice for healthcare professionals:

- PRES and RCVS present with the following symptoms: sudden severe headache or thunderclap headache, sudden onset of nausea and vomiting, confusion, seizures and/or visual disturbances
- PRES and RCVS are recognised very rare side effects with pseudoephedrine-containing medicines, which are used for the symptomatic treatment of nasal and sinus congestion with colds, flu and allergies
- pseudoephedrine is for short term use only and should not be used for prolonged or extended use
- use of the product is contraindicated in patients with severe hypertension or uncontrolled hypertension, or severe renal disease
- report suspected adverse drug reactions associated with pseudoephedrine on a Yellow Card.

Advice for healthcare professionals to provide to patients and caregivers:

- pseudoephedrine is used to relieve the symptoms of nasal and sinus congestion with colds, flu and allergies
- pseudoephedrine-containing medicines are for short-term, symptomatic use only; people should follow the instructions for use in the Patient Information Leaflet
- there has been a very small number of reports of PRES and RCVS with these medicines; PRES and RCVS are rare conditions that can involve inflammation and/or reduced blood supply to the brain
- if you experience a severe headache that develops very quickly or you suddenly feel sick or are vomiting, confused or experiencing seizures or changes in vison, then stop taking the medicine immediately and seek urgent medical attention
- do not take pseudoephedrine if you have very high blood pressure (hypertension) or hypertension not controlled by your medicines
- do not take pseudoephedrine if you have severe acute (sudden) or chronic (long-term) kidney disease or kidney failure. Speak to your doctor or pharmacist if you are unsure
- people who take a medicine may experience a non-serious side effect, and these are typically mild, but it is important to read the Patient Information Leaflet

that comes with your medicine and to talk to a healthcare professional if you are experiencing problems

Review of PRES and RCVS with pseudoephedrine

Pseudoephedrine is a sympathomimetic and is approved as a single active substance or in fixed dose combinations with analgesics, antihistamines, and cough medicines. Pseudoephedrine is used for the symptomatic relief of nasal and sinus congestion associated with the common cold and flu in adults and adolescents. It is also used for the treatment of the symptoms of seasonal allergic rhinitis in patients, including use in children aged 2 to 12 years of age who have nasal congestion.

There have been very rare reports of PRES and RCVS with pseudoephedrine. A review of the available evidence, including the assessment of cumulative reporting of adverse drug reaction reports, was considered by the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines (CHM). The PEAG recommended updates to the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) to further describe the risk of PRES and RCVS and the potential risk factors for these conditions, and advised the MHRA to remind healthcare professionals and patients of these risks.

About PRES and RCVS

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a rare condition in which parts of the brain are affected by swelling, usually as a result of an underlying cause such as severely elevated blood pressure, kidney failure, severe infections, certain medications, some autoimmune diseases and pre-eclampsia. The diagnosis is usually made by imaging of the brain, which may enable areas of swelling to be identified. PRES usually has an acute onset characterised by headaches and seizures; many people also experience visual changes, confusion and drowsiness, weakness of the arm and/or leg on one side of the body (hemiplegia), difficulty speaking, or more rarely other neurological symptoms.

Reversible cerebral vasoconstriction syndrome (RCVS), also known as Call-Fleming syndrome, is a rare condition characterised by thunderclap headaches which are sudden, intense headaches that can reoccur over a few days to weeks and are often associated with nausea and sensitivity to light. RCVS can also be associated with acute neurological symptoms such as seizure and stroke. Symptoms are thought to arise from transient constriction in the blood vessels of the brain. In some cases, RCVS may be associated with childbirth, vasoactive or illicit drug use, head trauma, autoimmune or blood disorders, or complications of pregnancy. RCVS is usually diagnosed by brain imaging with angiography, to identify constrictions in cerebral blood vessels.

For both conditions, patients typically fully recover within 3 months with early recognition and treatment.

UK reports of PRES and RCVS with pseudoephedrine

To date, the MHRA has received 4 Yellow Card reports of suspected PRES or RCVS with pseudoephedrine. This is in the context of widespread usage with over 4 million packets sold in the UK in 2022 alone.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme. Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

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Letters and medicine recalls sent to healthcare professionals in January 2024

A summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices.

Letters

In January 2024, the following letters were sent or provided to relevant healthcare professionals:

- Oral valproate-containing medicines: Restriction of indication for male and female patients aged under 55 years; use revised educational materials
- Omega-3-acid ethyl ester medicines (Omacor/Teromeg 1000 mg capsules): dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors
- Lagevrio® (molnupiravir) 200 mg hard capsules ▼ – Extended Use Beyond Labelled Expiry Date
- Artiss 2ml Fibrin Sealant [Human] (product code: 5500649): Interim supply of Nordic Stock (Norway/Denmark) to Mitigate Supply Disruption
- EXKIVITY▼ (mobocertinib) 40 mg hard capsules – Conditional Marketing Authorisation Withdrawal
- Veltassa 16.8 g powder for oral suspension (Patiromer): Interim Supply of Northern Ireland Stock to Mitigate Supply Disruption
- ADAKVEO (crizanlizumab) ▼: revocation of UK marketing authorisation due to lack of therapeutic efficacy as determined by MHRA
- Plasma-Lyte 148 and Glucose 5% w/v Discolouration
- Tostran (Testosterone, 2% gel): priming instructions in the current PIL require updating
- Tamiflu® (oseltamivir) 45 mg Hard Capsules: Different colour ink used on blister pack

Medicine Recalls and Notifications

In January 2024, recalls and notifications for medicines were issued on:

Class 4 Medicines Defect Information: Quadrant Pharmaceuticals Ltd, Cozaar 100mg film-coated tablets, EL(24)A/01. Issued: 4 January 2024. Quadrant Pharmaceuticals Ltd has informed the MHRA of an error with the Patient Information Leaflets (PILs) in the listed batches of Cozaar 100mg film-coated tablets. The PIL does not include the most up to date safety information. In Section 2 ‘What you need to know before you take Cozaar’, sub section ‘Cozaar with food and drink’ the following information is missing: ‘Grapefruit juice should be avoided while taking Cozaar.’

Class 4 Medicines Defect Information: USV UK Limited, Sugammadex 100 mg/ml solution for injection (2 ml vial), EL(24)A/02. Issued: 18 January 2024. USV UK Limited has informed the MHRA that Sugammadex 100 mg/ml solution for injection (2 ml vial), batch

number 35000347, may contain some vials that contain a low volume of solution; less than the label claim of 2 ml. Additional vials may need to be used to supplement the required dosage in line with the requirement of individual patient treatment.

Class 4 Medicines Defect Information: Cadila Pharmaceuticals (UK) Limited, Pantoprazole 40 mg Gastro-Resistant Tablets, EL (24)A/03. Issued: 30 January 2024. Crescent Pharma Limited has informed the MHRA regarding an error with the European Article Number (EAN) barcode on the cartons of the above-mentioned batches of Pantoprazole 40 mg Gastro-Resistant Tablets distributed by Crescent Pharma Limited. When scanned, the EAN barcode identifies the product as Bicalutamide 150 mg Tablets. Do not use these batches of medicine in robotic or automated dispensing or stocking systems and carry out manual dispensing and stocking, as appropriate.

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